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And you can see that in the multivariate analysis that -- if we look at time to breast recurrence and relapse-free survival that they tended to still be positive, but it was not statistically significant in this particular analysis.

So that's kind of interesting, but you stop there. One of the things that you'll notice is that we did not account for inhibitors. So as has already been alluded to, patients who have normal CYP2D6 metabolism who are taking Peroxitene have significantly lower levels of Endoxifen. And this is represented here in this chromatogram, which has already been referred to by Dr. Yasuda.

And here you see that -- from David Flockhart's group that plasma Endoxifen concentrations are significantly reduced in patients that are on weak or moderate inhibitors as well as potent inhibitors, such that you need to look at the patients that received -- who are wild-type that received Peroxiten, their Endoxifen concentrations really are about the same as patients who are a genotype poor metabolizer.

So when you think about that, you know it is actually wrong to try to look at the effect of genotype without accounting for inhibitors.

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Now, why is this important? Well, Peroxitene, Fluoxiten, Benlothoxin have been studied extensively to treat hot flashes in women who take Tamoxifen. And these drugs are very effective. They reduce the number and severity of hot flashes in Tamoxifen treating women.

Now, how often does this occur? Well, if you look at the current practice surveys, anywhere from 30 to 40 percent of Tamoxifen-treated patients are prescribed anti-depressants for either depression or hot flashes.

We also know that there are other commonly administered medications that also inhibit CYP2D6, such as Amioterone, Doxted, and Subenedine; such that when you look at this, an analysis of CYP2D6 metabolism in Tamoxifen-treated patients is really incomplete without accounting for inhibitors.

So when we firs analyzed -- when we first looked at the 893252 trial, we did not have the concomitant medication history. But we did obtain IRB approval. We went back. And we went back and obtained information at each randomizing site. We were able to get information on 225 charts, and what we did was to ask the question, did patients receive potent CYP2D6 inhibitors, such as Fluoxetin

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and Peroxitene or weak or moderate inhibitors such as Certralene, Cimetidine, Amioterone and Endoxifen, Tyclopanine or Haloperidol.

We looked at the duration of co-administration, we realized sometimes this is very difficult to look at because patients are seen once, twice a year. So we're asking simply did they receive the drug as best as we can say for less than a year, one to two years, two to three, three to four, or four to five years.

We then did an analysis where we defined CYP2D6

metabolism this way: we said a woman was an extensive metabolizer only if she did not carry a star four variant allele and she was not taking an inhibitor. Whereas, a patient with decreased metabolism was any woman who had either -- was either carried one or two variant alleles or could have any genotype and she was co-administered the moderate or potent inhibitor, and we simply said yes or no.

And in this analysis, we were able to get this information on 180 patients. And you can see that the median age of patients was 68; again, these are all ER positive tumors.

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Most of these are small tumors -- less than three centimeters. Most are lymph node negative and most are either grade one or two, which is the usual sort of patient population that we see.

Now, we note that if patient characteristics were similar, exactly the same as with those where we did not have this information.

So we were able to determine this in 180 patients. We found that only three patients were taking potent inhibitors, realizing the difficulties with this analysis. We found that 10 patients were taking moderate inhibitors, and that the median duration of use was two to three years.

And so here's time to breast recurrence, where we simply ask the question versus extensive metabolizers; that is, normal or absence of a star four and not an inhibitor versus those who either were genotypically poor or decreased or those who were taking inhibitor. And this was statistically significant.

Here's relapse-free survival; also statistically significant. And here's overall survival, where you can see that there's a definite trend towards worse outcome with a P value of .08.

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So then we did a multivariate analysis and now is the time to do a multivariate analysis where you've accounted for both the metabolism of -- excuse me -- you've accounted for both genetics as well as inhibitors.

And you can see that relative to extensive metabolizers, poor metabolizers had a 1.9 fold higher risk or shorter time to breast recurrence, worst relapse-free survival, and again a trend towards worse overall survival.

And this was statistically significant in the multivariate analysis after adjusting for tumor size, tumor grade, nodal status, ERPR and HER2.

So what I've showed you simply is an analysis between simply normal metabolism and decrease, but, as you can see here, the level of Endoxifen is really dependent upon potentially patients who are on inhibitors the levels depending on the potency of inhibitor.

So what we did was an analysis where we looked at what we defined as intermediate metabolizers. Now, this is a definition based on the information that we know.

So we called a patient an intermediate metabolizer if they were -- carried one allele, and they were not on an

inhibitor, or they were wild-type, and they took a moderate inhibitor. So there was eight patients in that analysis.

We defined poor metabolizers if they were genotypically poor or they could have any genotype and they were taking a potent inhibitor. There were nine patients that we didn't know simply because we didn't have both of those pieces of information available. And this shows you here time to breast recurrence as a function of the level of CYP2D6 metabolism.

And as you can see that poor metabolizers really have the greatest effect, and this is statistically significant and the log rate P value of .019.

Here's relapse-free survival. And one of the things I would point out to you here is that within the first two years, the chances of -- or the risk of relapse for death in patients who are extensive metabolizers is two percent versus about 32 percent if you're a poor metabolizer. And overall survival again was -- there was definitely a trend towards statistical significance with a log rate P value of .01.

We then did Cox modeling and what we're asking here simply is for patients who are poor or intermediate, we wanted to get a sense of what their risk was relative to patients who are extensive metabolizers. So this is Cox modeling, and this is analysis of our endpoints -- time to breast recurrence, relapse-free survival and overall survival.

And you can see, as you would expect, poor metabolizers have the greatest risk with a three -- over three-fold higher risk of recurrence compared to intermediate metabolizers using our definition and in relapse-free survival the same thing. And notice that in relapse-free survival, intermediate metabolizers definitely do have a trend towards worse outcome, but again this was not statistically significant. And in overall survival as well, poor metabolizers tended to have a worse outcome with a two-fold greater risk of relapse or death.

The last couple slides I want to show you are -- relate to studies that have actually already been done in the past.

One of the things that we've known for many years is that when women take the drug Tamoxifen, there is an increased risk of recurrence within the first two to three years. People have not been able to understand this. And this is actually an analysis of the ATAC [ph.] trial, which looked at the annual hazard rates of recurrence within the first -- well, within the six years of follow up.

And one of the things that was a very important finding from this trial was that Anastrazole smoothed this risk, so notice that within the first two years there you see this peak in the risk of recurrence for patients that are taking Tamoxifen, and for women who take the drug Anastrazole, this peak is reduced. It's not smoothed out. It's not eliminated. It's simply reduced.

So we did the same analysis. In our clinical trial, we looked at the hazard rates for patients who had decreased metabolism versus those that had extensive metabolism.

And what we found was that patients who had decreased metabolism we saw this same peak, but we noticed that for extensive metabolizer that that peak was reduced, and it was also shifted. So it was actually shifted out to somewhere near year four, and then it actually came down again -- versus for patients who had decreased metabolism that peak actually really does not come down, and actually there's been a second peak again at years six through eight.

So our conclusion is that in this trial CYP2D6 metabolism was an independent predictor of clinical outcome

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in post-menopausal women with ER positive early breast cancer and that the effect of impaired metabolism was most marked in poor metabolizer; and that we feel that these data are consistent with the pharmacologic data that have already presented that Tamoxifen activation to Endoxifen is dependent upon CYP2D6.

We believe that these data also suggest that determination of CYP2D6 genotype may be of value in selecting adjuvant hormonal therapy and that moderate or potent inhibitors of CYP2D6 perhaps should not be co-administrated with Tamoxifen.

I'm going to move -- before I do the last slide and describe an adjuvant clinical trial that has been proposed. This has been approved by the Breast Cancer Inner Group of North America and is actually right now at CTEP for consideration.

This particular trial is asking the question do patients who have normal or increased CYP2D6 metabolism, do they do better with sequential hormonal therapy than with patients who are treated with what many people believe is the standard of care, which is Aromatase inhibitor for five years.

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Notice that we are not randomizing poor metabolizers to Tamoxifen. So whereas, the label change here, you're asking whether or not women who are poor metabolizers should or should not receive Tamoxifen, we're not asking that question, and we believe that actually there might be ethical issues with that.

What we're asking simply is: in patients with normal metabolism, how do those patients do with receiving Tamoxifen, followed by an Aromatase inhibitor versus an Aromatase inhibitor at all. And this trial is powered to detect an improvement in the risk of relapse for patients who are extensive metabolizers.

In his trial, if patients are determined to be intermediate or poor metabolizers, they would be treated with what would be considered the standard of care, which is an Aromatase inhibitor off study.

So I'd just like to acknowledge obviously this work is not done in a vacuum, but it comes from a lot of people, most at the Mayo Clinic and the North Central Cancer Treatment Group, from investigators in the pharmacogenetics

research network and the COBRA [ph.] Group and also the funding for the Mayo Clinic Breast Cancer score. Thank you.

CHAIRMAN VENITZ: Well, thank you, Dr. Goetz. Any questions?

DR. JUSKO: Yeah, a wonderful summary. Thank you. Is there a correlation to ER and PR and CYP2D6, and the other question is, is there a relationship to quantitative estrogen receptor, which is and arguably may be more important than qualitative.

Is there a relationship, is there a linear relationship between 2D6 and quantitative estrogen receptors?

DR. GOETZ: We looked first of all -- first of all, when we did a multivariate analysis, we looked at the effect of estrogen receptor in a multivariate analysis. And we did not see an outcome.

In other words, we did not see, for example, when you looked at the quartiles -- and this, by the way, we did quantitative ER by chemistries. We looked at 0 to 25, or in this case, one to 25; 25 to 50.

We did not see a cut point that defined outcome in this particular trial. When we looked at PR, there was a -- there might be -- there might have been a slight trend, but it wasn't statistically significant.

We did not see -- and I don't believe that we have done the analysis which you're asking is, is there a correlation with outcome with CYP2D6 in each one of those groups, and I think that would be a sort of analysis that would require a lot of patients.

CHAIRMAN VENITZ: Okay.

DR. JUSKO: I'd also like to compliment you on some very excellent studies.

A couple questions about exposure of patients to the drug and various metabolites. Your chromatogram shows a very large peak for Tamoxifen, and it apparently has one one hundredth of the activity. The hydroxy metabolite has equal potency, and the other metabolites the NDM metabolites and such I didn't see data for its potency.

But I wondered if you did or could do a retrospective assessment of the relationship between efficacy and exposure to Endoxifen as well as the variety of metabolites, because it would seem that composite efficacy or your composite assessment would provide very insightful information.

And in relation to all of that, in consideration of this composite of different drugs and metabolites that have activity, it appears to me that Endoxifen has a greater share of activity than the rest. It seems like there's much more, a stronger relationship to Endoxifen than is apparent from all of these other materials that are present.

DR. GOETZ: So I think the answer to the first question, I would agree with you heartily. I think what we would really like would be a prospective clinical trial where women were randomized or received Tamoxifen for 20 --

or excuse me -- for five years, 20 milligrams a day, in which we had both genotype as well as plasma Endoxifen concentrations.

Unfortunately, there are no datasets that are out there with that sort of information. David Flockhart's dataset is really probably the largest, but there is no efficacy data on particular patients. They weren't followed for efficacy.

So I think that ultimately this is an extremely important question, and it's one of the questions that we will definitely try to answer in the prospective trial, where we will actually collect plasma samples on patients and to determine whether or not the relationship between clinical outcome does correlate with metabolism of

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Tamoxifen. It's a very important question.

DR. WATKINS: Just to make sure. I didn't get a copy of the Incress [ph.] article. But that's the same patients, the same group of patients that were in the first study?

DR. GOETZ: Absolutely. It is the same -- it's really an updated analysis. It's not a different dataset. What we are doing is analysis that we couldn't do initially. We didn't have access to, and that is to analyze the patient population with the inhibitors in mind.

DR. WATKINS: But the inhibitors was a very small percent of the population, right, that were taking them?

DR. GOETZ: The number of patients that were on inhibitors by the ones that we queried was about six percent. So, and part of this relates to, for example, when the trial was started back in 1989, patients who were taking Tamoxifen were not administered SSRIs, so it wasn't until around 2000, the late 1990s or in 2001 where this became common practice, and we actually had the data for Benlofaxin, for Peroxitene.

DR. WATKINS: Right.

DR. GOETZ: So when we looked at this, the numbers, for example, six percent is probably about what we would

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expect for that particular time period.

DR. WATKINS: Okay. And was there any new conclusion in the new smaller --

DR. GOETZ: Yeah.

DR. WATKINS: -- data subset?

DR. GOETZ: So in this particular data subset -- so for the first data subset, we had a total of 190 patients. The second data subset our actual analysis that we looked at was 180 patients where we clearly said we know the medication history of these patients. And our final conclusion with that is that once we've accounted for CYP2D6 genotype and inhibitors, and we've also done a multivariate analysis that accounts for the usual factors of tumor size, nodal status, tumor grade that CYP2D6 metabolism, as defined by what we saw was an independent predictor.

Now, really that -- the difference essentially is that whereas in a multivariate analysis before the findings were not statistically significant, and now they are.

DR. WATKINS: Okay. Thanks.

DR. GIACOMINI: A very nice presentation. So a couple of questions. One, and maybe you discussed it, but the Aromatase inhibitor and CYP2D6 phenotype, genotype that was discussed has not been involved?

DR. GOETZ: It has not been, and, again, as far as we know, CYP2D6 is not involved in the metabolism of Aromatase inhibitors. But no one has done that particular or asked that particular question or done that analysis.

DR. GIACOMINI: And would you do that in that study that's planned?

DR. GOETZ: Absolutely. Yeah.

DR. GIACOMINI: Put that on your schedule. Okay, and then secondly, when you have this group of people that you call poor metabolizers that those were CYP2D6 genotype and they also were in inhibitors, did you try to separate those out to see if you see a difference between the genotype and people who are on inhibitors?

DR. GOETZ: Right. So that's a really good question, and that was our hope initially when we did the study, but clearly when we looked at the patients who were wild-type; that is, they were at least by criterion of star four or lack of star four, and we asked whether those patients were taking an inhibitor, in this case, a moderate inhibitor, how did they do versus the other patients who were not on inhibitor. The numbers were just really too small to answer the question.

We had I think a total of eight to 10 of those patients in that particular category.

Now, interestingly, most of the patients that we looked at were actually were wild-type, were taking the inhibitors. And we -- I don't have the data in front of me -- but there was a clear trend towards worse outcome, but we didn't have the statistical power to answer that question.

DR. BARRETT: This may be getting a little bit ahead of ourselves, but I know when I look at your histogram here regarding the categories of plasma Endoxifen relative to the different inhibitors or genotype categories --

DR. GOETZ: I think this is David Gloghertz [ph.], so this is upgraded.

DR. BARRETT: Okay. Great. But I'm thinking clinically, I mean if I looked only at this you might be able to suggest that dose modification may improve, in fact, the clinical performance, but based on your analysis, would you see that as a reasonable strategy or you don't think there's enough information at this stage?

DR. GOETZ: I think the little information that we have from what I've seen from David Flockhart's data is that increasing dose probably does not improve the outcome. But I think that that would -- you know, you would need to do a study to look at that. And at this point, there's really no data on this specific group that would suggest that increasing the dose would improve the outcomes.

And I don't think that's really the question that's on the table. If Tamoxifen was the only drug that we had that

would be an extremely important question. The issue, of course, is that we have alternative drugs that are at least a safe drug and should -- slightly better than Tamoxifen, with a different side effect profile and so, although that's an important question, it may be an important question to ask about, say, in developing countries, where finances are limited.

I don't think we know that information.

DR. RELLING: When you were able to go back and get the concurrent drug information, did you summarize concurrent drugs that might affect CYP3A status, either inducers or inhibitors to see if there was any relationship there?

DR. GOETZ: That's a really good question. And the answer is no, and I wish we would have done it. And so we

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didn't do it at that time, and I think that's an extremely important question.

DR. MORTIMER: So the relationship of hot flashes to metabolism was established in your initial complication. Do you have any data for the favorable effects of Tamoxifen? I mean is there a correlation to bone density increases or uterine cancer? Do you know any data to that effect?

DR. GOETZ: No. We don't know. I mean but, you know, you certainly wonder, because if patients who are really being exposed to only the very weakest anti-estrogens are those women that perhaps get the least benefit perhaps in terms of bone effect, you wonder about lipids. You wonder about all the other secondary endpoints of Tamoxifen, and I think more and more data will come out and hopefully will clarify this in the future.

DR. MORTIMER: I am struggling a bit on our task at hand. You asked to specifically give a neutral conveyance of the data from your studies and you did that in a great fashion.

Stepping back from the neutral side and thinking about how you would apply this and say package insert change that we not vote on, since we're not officially voting, will

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affect you do you think the data that is available currently is sufficient to strongly encourage the use of CYP2D6 testing in the selection of Tamoxifen versus an alternate therapy?

DR. GOETZ: Well, I think that, you know, certainly I am biased because this is my own data, and so I think that as more and more data come in, for example, the data from the Italian Prevention Study, and other groups that look at this that are able to ask the question in the appropriate setting that I do think that this is important.

What am I doing right now, for example, in my clinical practice? I'm not going to patients and saying we should test all patients right now simply because right now when I see a patient, we are, you know, there's really two options on the table and one of them is Tamoxifen; and one of them is for Tamoxifen, and Tamoxifen for several years; another is Aromatase inhibitor.

So I'm not going to that patient and saying in order

for me to make this decision, I've got to use this test -- this particular test.

What I am doing, though, however, is I'm telling them the information, and I really try to be as unbiased as I can. This is what we know. And what women are often times asking me is I want to be tested based on this information, and the reason this is important I think is because we have options and the options are to use Tamoxifen for a short period of time versus all the time Aromatase inhibitor versus an up-front Aromatase inhibitor.

So, you know, to answer your question, am I doing it in clinical practice? I'm presenting the data, and when I present the data to women, some women are saying, gee, I would like to be tested, and other women are saying that they are not.

I think that as time goes along and more and more evidence comes in, though, that I think that I definitely would do the routine.

DR. LESKO: Matt, I have two questions and maybe I know the answer; you've given the answer.

But the first was there's been a number of presentations in which you've had on the Y-axis the Endoxifen plasma concentrations and on the X-axis various subsets of the patients, whether they're on inhibitors, whether they're on genotypes. Is there enough people in these subsets to define a minimum effective concentration of Endoxifen and begin to look perhaps at individual patients as opposed to these population means we see? That's sort of my first question.

DR. GOETZ: I think the answer is that, you know, for poor metabolizers, my gut feeling is that those patients are not getting enough Endoxifen. But I don't have -- 'cause I don't have studies that correlate those plasma levels with the clinical outcome.

So we're doing this by means of CYP2D6 genotype. So what I do believe, however, is that the analysis -- and some people have done the paths, which is simply lumping together star four wild-type with poor metabolizers and asking maybe those patients do worse, and they simply do this, but they don't have enough poor metabolizers. I think you cant' do that, and I think there's not enough data at this point to clearly say that patients who are intermediate metabolizers should be denied, although there's certainly that -- there's some data that would suggest that. I don't know if that answers your question.

DR. LESKO: It seems like an analysis that would be done such that people might monitor blood levels.

DR. GOETZ: Right.

DR. LESKO: Either as an alternative to genotype or in addition to genotype.

DR. GOETZ: Right.

DR. LESKO: As an adjunct piece of information.

DR. GOETZ: Right.

DR. LESKO: Secondly, I just wanted clarity on. When

you looked at the 225 charts, you lumped together into the 2D6 poor metabolizers four fours as well as wild-type star fours, in other words, homozygous star fours. Is that because there wasn't enough star four star fours in those charts?

DR. GOETZ: Sure. What we defined in that trial was a patient was a poor metabolizer even by virtue of genotypes and they were star four, star four, or they were actually taking a potent inhibitor.

So the only way that you could be defined as a poor metabolizer if you were either genotypically a poor metabolizer or we actually also said if you were a wild-type star four, and there was also -- there was one patient that was wild-type star four that was taking a potent inhibitor, and then there were a number of patients that were -- had normal metabolism or taking potent inhibitor.

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So that was that definition.

DR. LESKO: Okay. Thanks.

CHAIRMAN VENITZ: Any other questions? Well, let me ask you a couple of questions as well.

You're aware of the Nowel study obviously, because it seems to conclude the opposite of your study and some other studies as well.

Do you have any explanation for that?

DR. GOETZ: So. Yeah.

CHAIRMAN VENITZ: Which is going to -- not only does in not confirm what you found, it actually goes in the opposite direction.

DR. GOETZ: So I would say two things: for both the Nowel study and the Glickman study, first of all in that -- in those patient populations, they used -- 35 percent of them were ER negative.

So, for example, the Nowel study 35 percent were ER negative.

We know that Tamoxifen is ineffective in ER negative.

The second thing is that it was a retrospective analysis of patients that were stage one, stage two, stage three, and stage four. Okay?

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And so when you do that sort of analysis, you know, you're -- you have such a varying presentation.

What we're simply asking here is in the adjuvant setting, so patients have stage one through three.

The third thing I would say is that in that particular study again is it relates to the primary endpoint, which was distant relapse free survival, and also the Wegman trial and, you know, it has to do with when you follow these patients, where are you censoring them? So, for example, if you're not accounting for what would happen to the clinic if a woman's on Tamoxifen -- let's say she has a local relapse, we consider that a failure of Tamoxifen, and we don't wait until five years later when she develops a distant relapse. The same with contra-level breast cancer.

So if you don't account for all of the endpoints which really confer response to Tamoxifen, you're going to have difficulties.

So I think just -- when you look at just those issues there, and then also probably the last issues, the number of poor metabolizers was probably in the range of three to four I think in both of these trials, very small.

And so the tendency is to say, well, we don't have

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enough, let's just lump them in.

The final issue is did you account for concomitant medications, and, as I showed you in our study, medications made a difference in terms of our analysis and so forth.

CHAIRMAN VENITZ: A separate question, but somewhat related, too. Of all the studies that I've seen and these were in the adjuvant setting, what about hemo prevention. First of all, how much Tamoxifen is used in that setting and are there any data -- outcome data or exposure data?

DR. GOETZ: So the only data that is available is from the Italian Prevention Study and this was published in a letter to the editor several months ago in the Journal of Clinical Oncology, and what they found was that women who took Tamoxifen and who developed breast cancer had a significantly higher frequency of the poor metabolizer phenotype than those women who did not develop breast cancer -- so -- and who also took Tamoxifen.

So I think the data there support all the findings to date, but I think they're relatively limited, and so obviously that's a very important -- and it's very important because when you look at Tamoxifen versus Reloxifen, really what you have is a comparison of a weak anti-estrogen with a

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weak anti-estrogen. And one drug is activated. One drug is not.

And so if you -- if you're giving Tamoxifen to prevent breast cancer or high-risk patients, and what's happening in the clinic today is that 40 percent of those patients are receiving inhibitors of the enzyme, you could essentially make the drug another Reloxifen just by simply by using the medications.

So I think that that's a very important question.

CHAIRMAN VENITZ: So how large is the use of Tamoxifen in that setting as opposed to the adjuvant setting?

DR. GOETZ: Well, in the prevention setting, you know, it's been the only drug that's approved. You know, Reloxifen, I'm assuming, may become approved in the future, and I think based on, you know, the studies, the Reloxifen trial I think -- Reloxifen versus Tamoxifen and that's obviously a viable alternative to Tamoxifen for patients who are at high-risk.

And I would note that in that trial, Reloxifen versus Tamoxifen, that was only in post-menopausal women. So in pre-menopausal women, we only have one drug available, and that's Tamoxifen.

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CHAIRMAN VENITZ: So if pharmacogenetic testing were to be used to rule out the use of Tamoxifen, there wouldn't be an alternative for pre-menopausal women?

DR. GOETZ: That would be correct. As far as I know, there's no other drugs that are used for pre-menopausal

breast cancer prevention.

CHAIRMAN VENITZ: Then the last question in the study that you gave when you started this prospective study to look at the effect of genotype, how are you going to handle the effect of inhibitors?

DR. GOETZ: Well, in that particular trial, we will not allow women on the trial who are taking potent inhibitors up front. What we will do, however, is that for patients that are on the trial and in which a potent inhibitor is medically necessary, we will definitely allow those patients to take the drug. They will be encouraged not to be on a potent inhibitor, but let's say, for example, that medically it's necessary. They are not responding to a non-potent inhibitor. We would not prevent them from getting it. We simply -- we will definitely account for those patients.

We haven't decided as of yet whether those patients

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would be censored or not. That's a good question.

CHAIRMAN VENITZ: Thank you.

DR. JUSKO: I hope you don't think this is a silly question, but in your -- one of your publications you indicate that 61 percent of women experienced hot flashes, can you use hot flashes as a biomarker, you know, titrate against how women experience hot flashes and then backing off when they do?

DR. GOETZ: I don't think so, 'cause I think hot flashes are really variable. I mean I think the Tamoxifen, you know, this observation that we made with CYP2D6 and hot flashes certainly was interesting, but it needs to be corroborated by other people.

I think it is concerning, though, obviously that we've acknowledged or we've viewed hot flashes as being evil, and we've tried to prevent hot flashes.

And obviously this is important because if you're taking the drug and the hot flashes are so severe that you can't take the drug, you have to go off of it, well, that's just as important as if you were a poor metabolizer.

So I think that a lot of more research is needed in this area.

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DR. MORTIMER: So 30 percent of all breast cancer patients are on an alternative or complementary therapy at least. Are any of these 2D6 inhibitors?

DR. GOETZ: I'd have to defer. I'm not aware of that, and I think simply we don't know. I think the answer is we don't know.

You know, for example, you know, the question of 3As come up. Obviously, there are a number of 3A drugs, such as St. John's Wart that are inhibitors. That potentially might be important.

But I think there we just don't know.

OPEN PUBLIC HEARING

CHAIRMAN VENITZ: Okay. Thank you again for your excellent presentation.

Now, we're moving on to the open public hearing, and I'm going to read this following statement on the record.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payment of your travel, lodging, and other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you chose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Having said that, I'm going to ask our first speaker to give his presentation. Ryan Phelan from DNA Direct.

MS. PHELAN: Hello. In the spirit of full disclosure, my company, DNA Direct, provides genetic testing services to the public.

We're based in San Francisco. We are in effect a web-enabled genetic counseling service. We are not the lab.

We work with national reference labs, pre-certified labs, and we provide the interpretation, both the pre-test and education. We help people identify if testing is appropriate, and then we help them really understand the impact of their test result in the full context of their health care situation.

We started our testing around clinically valid, medically well-known tests, like Factor V in cystic fibrosis, and we're in the process of looking at pharmacogenetic testing very seriously.

The first test that came to our-the first drug that came to our attention that had the most significant correlation with patient outcomes in terms of effectiveness of drugs was in the case of Tamoxifen.

And I'm here today to say that the research that we did, which included experts from around the country, indicated to us that there is very poor awareness of this correlation, and that one of the things that I can really urge this committee to do is to think about the impact that labeling has. It's the first step of really bringing public awareness of the fact that genotyping in the case like this may have tremendous benefit to women.

We started our research with an oncologist, Anne Rene Hartman [ph.], and Dr. Paul Helth [ph.] at the University of Indiana, who's also an ethicist, to raise the question of when is testing appropriate for women.

And I'd like to just put one human face on this. We've seen a lot of numbers here today. There are over 500,000 women today on Tamoxifen, and whereas Dr. Goetz mentioned, I'm sure quite accurately, that the standard of care includes the Aromatase inhibitors increasingly as part of therapeutic practice today, you can count on many medical centers today only offering women Tamoxifen, and many insurance plans only reimbursing Tamoxifen. It's one-tenth of the price approximately of an AI.

So there are women out there who are taking drugs and in some cases it is as good as taking a placebo.

Our recommendation to this panel is that you recommend the re-labeling of Tamoxifen now for post-menopausal women because there are no treatment options. Certainly, they can sequence the Tamoxifen, as we've seen with two years of Tamoxifen, with genotyping to verify that they're going to be a proper responder and follow it with an AI therapy.

In addition, they can also go on AI alone, which is

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certainly an appropriate pre-men recommendation for 2D6 for a metabolizer.

We believe that testing for Tamoxifen will enable women to make more informed treatment decisions about Tamoxifen and hopefully really avoid them taking potentially ineffective therapy that really increases their risk of cancer.

We believe ethically, it's irresponsible not to re-label this drug.

But our second position is that it has to be very clear that we're only talking about post-menopausal women. We've hardly talked about pre- and peri-menopausal women where the data is not yet in. These women do not have a known, safe alternative. They cannot go on Aromatase inhibitors.

So our company is preparing, based on this hearing today, to offer this test. We believe that, with our partnership with one of these labs, that we can bring this test to market for our total cost of less than $300 or approximately $300. This is not an expensive test for any medical center, any physician to be offering. Without our services, they could bring that price down probably to $200.

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So we really feel that this is something that is important for this Committee to address, but certainly more research is needed around what alternatives are appropriate for pre- and peri-menopausal women.

We believe that research should be fast tracked in this area. Women should not be on this drug if it's not going to be effective. Even if there is no known alternative, they should know that it may not be effective for them.

What we've done right now is we've started a -- we've just had an IRB approval with the Greater Baltimore Medical Center for a very small study on the chance that this committee is requiring more research on Tamoxifen. This was just approved for genotyping of a retrospective data, and

DNA Direct will offer free interpretation and free testing to this group of a hundred women.

In addition, we have talked -- and it's really in very early discussions with Sloan Kettering about again trying to fast track a retrospective study for pre-menopausal women and to again offer or donate our services for genotyping and what we really do, which is the test interpretation.

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So, in closing, I'd really like to just reiterate my hope that today you think about these half a million women who are taking this drug, a hundred thousand women that could be put on it this year alone, and ongoing, and really think about safe and effective therapies. Thank you.

CHAIRMAN VENITZ: Thank you. Our next speaker is Dr. David Flockhart from Indiana University.

DR. FLOCKHART: Good morning. I'd like to thank the Chair so I could speak.

And my principal conflict of interest I have to declare is the research lab that keeps me going.

I have a lot of questions I'd like to address, and I'd like to do it in an overview kind of way so that I can be quick.

But really, fundamentally, this derives from what Dr. Pazdur said and that's having good quality science to support the label changes that you'll make. And we haven't talked about what's in the label at the moment. And I think that is important to consider.

But there are no data, accurate data, but accurate data about term metabolism is not on the label. There's no data about drug interactions, rational at present in the

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label, independent of the decisions the Committee has to make about genotype.

The quality of science going into the work, I think, as I hope Dr. Goetz has been clear here, we're presented with three, four, or five trials here, and the quality of those trials is different. We do prospective randomized trials for a reason, because we can't independently separate out in a disease like breast cancer the prognostic from the therapeutic. So, for example, if people have lymph nodes, they are more likely to have a bad prognosis, and in the Nowel and the Wegman trials, they went into these studies in a non-prospective or retrospective way, and the groups of people that they compared are not small in terms of the number of lymph nodes that the have, the stage of the cancer -- is it one, two, three, four -- or the progression of the disease or the pathology. None of that is randomized.

And so part of the reason Dr. Goetz spent so much time on a multivariate analysis of the last trial was that it's the only trial that it's the only trial that's possible to do a multivariate analysis on. When you do multivariate analysis, it still comes out as a useful guide.

I want to quickly go through a series of questions,

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excellent questions, from the Committee.

First, Dr. Howard McLeod's first question about whether 2D6 has an effect on prognosis of a tumor after you

got the data that addresses that.

There are two pieces of data that address that, I think when you confidently say people who have breast cancer or who develop breast cancer do not have a different 2D6 genotype from people who don't, and that there are several studies that we use that show that. But that's really only half of Howard's question.

Howard is really asking does it affect prognosis or treatment, because Dr. Goetz did not include a no treatment arm, even when it was done. And, in fact, that is a completely rational scientific question. There's no biological or pharmacologic basis to believe that 2D6 might affect prognosis in the absence of a drug. But Howard is absolutely right. Biology constantly surprises us, and it's possible. So it's something our group is interested in, and we have an ongoing collaboration with Baylor to look at the famous samples of blood during the Baylor flood to compare non-treated to treated in that group and see if that's possible.

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Howard is absolutely right of asking the question.

Protein binding we do know from way back -- it was the question over here, and it's the same for the metabolites. Bill Jusko -- excellent question -- can you model the concentrations, and you're absolutely right. There's a very high concentration of Tamoxifen compared to these active metabolites. It's 10 to a hundred times more, so it's very reasonable to ask the question, could it actually be contributing to the therapeutic effect.

And so Dr. Desta has done a careful modeling analysis, including both potencies and the concentrations, as things state, and when you do that Endoxifen still jumps out as the greatest variable predicted.

And I should say in parentheses that people have gone in and done this crazy thing of biopsing tumors, and measuring concentrations in the tumors of Tamoxifen that is metabolized out of estrogen, and then saying, well, oh, because there's so much stuff in there that it almost saturated. And really that to me, that's always been an irrational approach, because you're getting total tumor and some of that is unavailable to anything; some of it is potent, and you really don't get an idea of that, of what is

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the concentration that affects that.

So you have to model these things, and we don't need to know it, but the modeling exchange is important.

Kathy, Mary, and a bunch of people asked questions about increasing the dose. As you increase the dose of the Tamoxifen, and this was shown in studies in the U.K. a long, long time ago, 20, 30 years ago, you don't increase the efficacy of the drug, and we believe that's because as you increase the concentration of Tamoxifen, you do not increase the concentration of the active metabolites for the drugs, because of this saturation. In other words, we have Tamoxifen concentrations going up and up and up, but Endoxifen and 4-hydroxy Tamoxifen concentrations do not go up. They saturate quite early, and this is the basis for a

lot of interest in Europe, in particular in Italy, of using very low concentrations of Tamoxifen metabolite, the same concentrations of Tamoxifen is possible as a therapeutic alternative.

Inducers, which several people asked about. Inhibitors in our data only slightly changed N-desmethyl concentrations, and inducers, to our surprise, and this is an important thing to understand, do you turn on metabolism.

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Do you make more Endoxifen and, therefore, might you get more therapeutic effect?

So we looked at the very small number of patients who happened to get inducers and look at all these numbers in our trials. And to our amazement, these are the patients with the lowest concentrations of Tamoxifen.

So we would anticipate, we have St. John's Wort and other inducers would actually lower the concentrations of the active metabolites because of distal induction. They turn on Sulfatransferases. They turn on a lot of transporters as well, so what inducers do is very complicated. But we don't think that it gets consumed.

A question was asked about other phenotypes, if you like, of Tamoxifen effect, and we have data that was presented two years ago by Anne Wynne from our group and others showing that there is a clear statistical fact of 2D6 genotype on bone density when patients are on Tamoxifen. We also have more recent data submitted to the Clinical Pharmacology meeting showing the same thing for clearance.

Full disclosure we did not see that. It seems to follow a different mechanism, but we don't seem to see it as having he same 2D6 effect.

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So I think to close, the science here I think supports going in carefully to the clinical trials, but I want to end on a note of caution for the Committee, and that is really what Dr. Goetz and the Mayo guys have done is really remarkable in that they been able to go back and look at a level one study, a prospective trial and show that not only is there a genotype effect within that, but there's a drug interaction in that effect that we can predict, and we would anticipate that this is a very important thing, because so many patients now, 20, 30 percent of patients with breast cancer, are taking some kind of anti-depressant. So the drug interaction is really important I think.

The note of caution really is this: we have excellent level one data from one good study, and that's really what we have to support the idea that genetic prediction using 2D6 could predict outcome. And while the tea leaves are that the Italian trial is going to show the same thing. We have one letter to the editor showing that, and there's apparently a trial in Germany that is showing some of that. We do not have a large number of prospective trials to look at. Probably, there will not be prospective trials done on Tamoxifen versus placebo. One couldn't get that, and

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probably we will have to rely on the kinds of studies that one gets to go through which is to know prospectively. I'll

stop there. I'd like to take questions.

CHAIRMAN VENITZ: Are there any questions by the Committee?

DR. BARRETT: Dr. Flockhart, you were mentioning about the -- in answer to Dr. Jusko's original question about the modeling the dose exposure relationship and the fact that you could -- you were able to resolve all of those, the active moieties and you could make predictions. And you also mentioned that the fact that there is information about the saturability of metabolism so that dose increases were unlikely to improve clinical outcomes based on that.

And one of the things that Larry had mentioned earlier was this concept of a minimally effective concentration. If you have this kinetic signature well defined, you could I think do some of that retrospectively and I would -- and also based on Dr. Goetz's presentation that, you know, you have the priors assembled, although it's from different sources, to really simulate that trial, that prospective trial. I mean there's going to be assumptions that had to be made there, but I think the technique exists to do this.

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You've got 1,950 people in each of those arms, which seems like a lot. I'm sure the sample size calculation isn't justified based on the --

DR. FLOCKHART: I totally, totally agree with you. You could absolutely and you should.

DR. MORTIMER: I'm sorry. Could you repeat what you said about bone density?

DR. FLOCKHART: About bone density. So if you take -- and we now have about 200 women, but the published data is on about 80 women. And when we looked at 80 women, post-menopausal women based on Tamoxifen, and looked at the effect of 2D6 genotype on the change in bone density that occurred in those women, there is a greater change in patients who have extensive metabolite status versus who have poor metabolite status.

DR. MORTIMER: The change being improved bone density?

DR. FLOCKHART: No.

DR. MORTIMER: So it's the opposite of what you're saying.

DR. FLOCKHART: I'm sorry. I'm going to get this wrong. I need Nina to come up here, but in -- there's two

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things in that study. One is a genotype effect, but the other thing is there is also a relationship because we were able to do this between Endoxifen concentration and the change in bone.

But if I get this right, post-menopausal women you put on Tamoxifen; right? It's protective, so you see a more protective effect in extensive metabolizers, correct? I got it right. And a less protective for poor metabolizers. You see the opposite effect in pre-menopausal women, which is why I was emphasizing the difference.

DR. WATKINS: Yeah, David, just congratulations to you and your collaborators on a terrific story.

But I would like you to elaborate a little bit,

because you tell me the estrogen receptor is inside the cell, so really concentrations outside the cell are irrelevant, and correct me if I'm wrong about this, and can you elaborate a little more on what the evidence is that Endoxifen is the major intracellular estrogen blocker and follow up on Kathy's comments about active transport, please?

DR. FLOCKHART: Well, there are a lot of things we don't know here, but I don't think the extracelluar

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concentration is irrelevant; right. It's probably the best surrogate for effect for many, many drugs for which we don't have intracellular concentration available.

So what we do is we look for effects of drugs that we related to pharmacogenetics. That's the whole field of pharmacogenetics, because we have something to measure; right.

So I think one would presume in this context even for steroids, and Bill Jusko has done this kind of work, has looked at steroid concentrations in the plasma and then related to them to sensitive measures of steroid effect in the adrenal access and things like that.

Actually, measuring the stuff inside is really hard to do, so what I'm about to say involves a series of assumptions, because anybody has to make assumptions to make any scientific, rational statement about what's inside the cell.

But if you look at affinities, the tightness of binding, for the estrogen receptor, and you make the assumption that the concentrations inside have the same relative size as the concentrations outside, so you assume, for example, that the ratio of Tamoxifen to N-desmethyl is

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the same, and that the ratio of N-desmethyl to Endoxifen is the same. And that's a big assumption and Kathy could jump all over me, because things might alter that.

But if you do that, if you make that big assumption, Endoxifen jumps out as the most potent thing that would be binding to the estrogen receptor and also -- and there's important pharmacology here I think -- that the efficacy of the drug would vary according to estrogen concentration, and we know that that's true, because we know that Tamoxifen is not a -- it's a bit like a beta blocker in the sense of its' not an absolute -- its' a partial antagonist. It's not an incredibly effective thing, and so you see different effects of the drug as I just referred to in pre- and post-menopausal women, when presumably the concentrations of Tamoxifen is metabolized the same, but the estrogen concentration is different. So this would indicate that if you change the estrogen concentration, you can alter the effectiveness of he drug indicating in turn that the concentrations of anti-estrogen metabolites might alter effect, because if you change estrogen, you could change the effect. So it's not -- I don't -- prominently it can be altered by estrogen. A complicated answer to a simple

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question, but I'm afraid it's not really a simple question.

CHAIRMAN VENITZ: Okay. Thanks again, David.
We are now proceeding to our main order of business; that is Committee discussion and questions, and what I'd like to do is maybe ask Atiq to pose the questions again, so we can look at them one at a time.
DR. RAHMAN: Okay. The first discussion point that we have today is to address the issue that the scientific evidence on metabolism of Tamoxifen demonstrates that CYP2D6 is an important pathway in the formation of Endoxifen.
CHAIRMAN VENITZ: Okay. Any comments? Any discussion points?
Does anybody disagree with that statement? So we cannot vote, but nobody disagrees; right? Okay.
Let's move to question number two.
DR. RAHMAN: The second discussion point is the pharmacologic and clinical evidence are sufficient to demonstrate that Endoxifen significantly contributes to the pharmacologic effect of Tamoxifen.
CHAIRMAN VENITZ: Any discussion? Does anybody disagree with that statement?
DR. RELLING: I mean it's clear -- the in vitro data

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look very strong, but are there clinical data that we talked about to support that?
DR. RAHMAN: This would reflect the inhibitor studies and the studies which Dick Flockhart's group have shown in 80 patients and 156 patients showing that the levels are down in genotype patients, as well as patients who are on one tab, but getting the strong inhibitors.
DR. RELLING: I definitely believe that 2D6 contributes clinically to the levels of Endoxifen, but as Dr. Jusko is asking for are there clinical data to indicate that the levels of Endoxifen relate to clinical effect? I mean.
DR. RAHMAN: That is the second -- that is the next question I think we were saying.
DR. RELLING: Well, let's see. It contributes to the pharmacologic anti-estrogenic effect of Tamoxifen?
DR. RAHMAN: Right.
DR. RELLING: I guess I think if it said the pharmacologic evidence is sufficient to demonstrate, then I think it's non-controversial. But if we're asking to say that there's clinical evidence that Endoxifen significantly contributes to the pharmacologic anti-estrogenic effect of

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Tamoxifen, did we review anything on that or does such data exist elsewhere that we didn't review?
DR. MCLEOD: It certainly looks like Endoxifen is the leading candidate for that endpoint based on the data that was presented, but I agree with you; there was no direct data saying that Endoxifen levels or Endoxifen itself is the or a major contributor to the clinical effect.
In my gut, I believe it is, but, based on objective evidence, it --
DR. BARRETT: I think you have a bridge here between the trials in which you have genotype as a correlate to a clinical effect, and then the work of the Flockhart

laboratory in which you're looking at the genotype exposure relationship, so I think that's the bridge -- I would agree, Howard, there's no single study that kind of looks at that so you have to mentally be able to make that bridge. But I felt that the data was compelling at least to be able to make that conclusion. I don't know what the rest of the Committee thought.

DR. JUSKO: I think there are strong indications that this may be so. What we would like to see typically in clinical pharmacology is a concentration response

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relationship. We sort of have that implied in the fact that patients with lower Endoxifen concentrations are the ones who survive for a shorter timeframe, but it would be nice to strengthen that evidence with direct indications of concentration response relationship.

CHAIRMAN VENITZ: And I would add I don't disagree with the statement the way it's worded, because it says significantly contributes, so it doesn't tell me that it's the major contributing factor.

But I would point out, as other people have done before, the role of the 4-hydroxy metabolite, which is equally potent, obviously complicates it.

Any other comments?

DR. MCLEOD: I'd just point out as we -- this question to me has nothing to do with the question of what should be put in the package insert. And so, while there's still some -- there's still a bit of a black box around this, I think when we get to the next questions, we can vote or not vote more clearly.

CHAIRMAN VENITZ: Any other comments to question number two?

DR. LESKO: Yeah, just an additional comment, because

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we have sort of touched on really two issues of Endoxifen levels, one from the standpoint of genotype and its relationship to some of the outcome studies we've seen. And the other is the drug interaction question, and we are not -- at least for the drug interaction question, we're predominantly looking at the Endoxifen levels as a surrogate for clinical outcome.

It's not unusual, and I would say I wish we had all the time concentration response relationships, and it may or may not be possible to have that in this drug in these clinical outcomes.

But in the absence of that, we generally try to look at the exposure of what we believed to be the predominant pharmacological species, and do that basically in all of our special population studies.

DR. MCLEOD: Larry, that's a really important point to go on the record, because many of these examples don't have the sugar daddy to conduct, to afford to be able to conduct the studies that might be done with a new chemical entity. And we may never have that data for the majority of the examples that are going to be going forward. And, as a committee, we may have to look at this data slightly

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differently because of that. The, you know, perfect of good -- or whatever the Voltaire saying is -- is going to come into account more often than we would like it to.

DR. LESKO: Yeah, and I think the Committee and others realize we make many decisions with exposure, ranging from the approval of generic drugs to adjusting doses for new molecular entities, so it's not unusual to take blood level as a surrogate, if there's reasonable evidence that there's a mechanistic or causal explanation in relating in exposure of a chemical to some clinical outcome.

CHAIRMAN VENITZ: Any further discussion of the question?

Okay. Then let's move on.

DR. RAHMAN: The next question that we're asking the Committee to address or discuss is, does the clinical evidence demonstrate that post-menopausal women with ER-positive breast cancer who are CYP2D6 poor metabolizers are at increased risk for breast cancer recurrence?

CHAIRMAN VENITZ: Any discussion? Can I ask a clarification question?

It says 2D6 poor metabolizer. It doesn't say variant of I-type versus drug interaction. Is that by intent?

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DR. RAHMAN: This is by intent.

CHAIRMAN VENITZ: In other words, I read the question right now, poor metabolizer could be a genetic deal -- a genetic poor metabolizer or a drug interaction poor metabolizer.

DR. RAHMAN: It could be -- the phenotype that you're talking about, whether they're based on genetics or they're based on a combination of variant alleles and inhibitors, we could go with that, too, because the data were presented that support that.

CHAIRMAN VENITZ: Well, to me, it makes a big difference.

So I think we have the answer. It refers to both. Whether it's genetically or due to a drug interaction, we're talking about poor metabolizers.

DR. RAHMAN: So we are including CYP2D6 poor metabolizer phenotype? Does that clarify it?

CHAIRMAN VENITZ: Phenotype, yes. Phenotype.

DR. LESKO: I wonder, though. It's a good question, and I see the vagueness to it, but would it make sense for the purposes of discussion to separate those two out because we've seen datasets where the genotype was linked to outcome

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alone, and there was also datasets in today's presentation where genotype was combined with drug interaction data.

Mechanistically, I think we've seen that -- the same thing results, but for the purposes of discussion, it would be better I think maybe to separate out those two issues.

CHAIRMAN VENITZ: What does the Committee hear? In my mind, they should be linked, but I can't speak for the Committee.

Do you think we should have a separate discussion of the drug interaction related to poor metabolizer status or the genetic difference? Howard?

DR. MCLEOD: The only study that we can really talk about in the context of this specific question had both bits of information. The question that has to do with chemo prevention as far as I know did not have that data, at least it wasn't presented in the letter in the Journal of Clinical Oncology, so in the context of this question, they're so heavily linked I'm not sure whether we really can separate the issues. I mean there clearly was an additive value with adding those six percent of folks with the drug interaction, but, you know, really we're talking about the same group of patients. I'm not sure we can separate them clearly.

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DR. MORTIMER: I think they're definitely linked to the hypothesis about Endoxifen, but I really have trouble. I mean I think they should be separated because to rely on sort of retrospectively going back and knowing what drugs patients are on I think is very risky because, you know, if you look at the 30 percent of women who are on complementary therapies, less than 10 percent of their physicians knew that they were taking it. So I think the number of people who were taking over the counter Cimetidine, there's just no way. I think the data is less robust when we're looking at, so I think they should be separated.

CHAIRMAN VENITZ: Well, let me make you a counter argument: if you look at Dr. Goetz's initial analysis, the multivariate analysis, not incorporating the inhibitors, he didn't find a significant difference. He only found a significant difference in terms of the outcomes that he was looking at when he combined the genetic -- the genotype with the drug interaction, the phenotype.

So, to me, that's the reason why I believe they are linked, and, as far as labeling is concerned, I don't see how he can -- if that's what the Committee would advocate. If you can advocate through genotype, but then not consider

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the fact that other drugs that the patient might be taking on would have the same effects, both in terms of the exposure, as well as in outcomes.

DR. MORTIMER: It was significant for relapse resurvival, though, so the endpoint -- there is a statistical significance for one endpoint, one survival endpoint. The ultimate, the more important one, it's fascinating that you can -- to show that, but there is a statistical significance.

DR. BARRETT: I agree in terms of, you know, the contributions to that outcome measure, but I also think, as was mentioned earlier, that you need to decouple it in order to give practical guidances in terms of applying this in the label, plus I think even, you know, not falling in the category of focusing on a P-value, you still have compelling data that the genotype alone would support that effect, but I think the wording can be massaged to get it correct so that you represent both pieces; but I would still decouple it, so you can apply it easier.

DR. GIACOMINI: Yeah. I thought -- I don't know, but I thought he showed that the effect was on poor metabolizers -- you had to be a poor metabolizer with the drug. But if

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you just took the drug alone, the inhibitor drugs, on the extensive metabolizers, you're not seeing an effect. Can I ask you -- it was on the poor metabolizers?

DR. GOETZ: So in the univariate analysis --

DR. GIACOMINI: Okay.

DR. GOETZ: -- in our initial analysis, what we did a univariate analysis, looking at log rank P-value, time to rest recurrence, and relapse-free survival, disease-free survival were all statistically significant. When we looked at those endpoints, for example, relapse-free survival in the multivariate analysis without inhibitors, the P-value was .08.

When we analyzed this by accounting for the potent inhibitors, in the multivariate analysis, patients both with decreased as well as when we separated out poor and intermediate, there was a statistically significant -- an effect in the multivariate analysis, and I would note that second multivariate analysis, we actually went back and added additional factors, so whereas before we added nodal status and tumor size, we also looked at tumor grade, and we also did ER. We also did HERT2 [ph.], which we hadn't had available because we went back and assayed all those.

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So the genotype alone was the Journal of Clinical Oncology paper; the multivariate analysis, the P-value was .08 for nodal status in tumor size.

CHAIRMAN VENITZ: That's the discrepancy I was referring to; that the original multivariate analysis, just looking at genotype accounting for two or three prognostic factors, did not achieve statistical significance. But the multivariate analysis that was presented today that incorporated the inhibitors as well as other prognostic factors then showed a significant difference in our case.

Any other comments? Dr. Relling.

DR. RELLING: I guess I -- for the reasons we just heard and also what we know about CYP2D6 status, so, you know, 15 or 20 years of studies show that this is a polymorphism where there exists clinically used agents that are able to turn an extensive or intermediate metabolizer into a poor metabolizer functionally, and so it's an example where concurrent drugs is really an important thing to take into account when deciding somebody's 2D6 status.

So for the reasons that it's been so carefully looked at by the investigators and that everything we know about pharmacology suggests we should consider concurrent drugs

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that I would have no trouble leaving them coupled, and I think that the labeling could be changed to be more informative for clinicians by considering concurrent drugs.

DR. DAVIDIAN: Just as a statistician, I just want to remind everyone that even though the evidence seems very compelling to me, I still note that the sample size is very small. And so I just want to make that cautionary statement.

CHAIRMAN VENITZ: I'm not sure whether we have consensus of defining poor metabolizer as phenotype

regardless of whether it's genetically or as a result of drug interaction. For the purposes of question number three, we haven't gone through the sub-questions yet.

Then let's discuss the merits of the question. The question is does the clinical evidence demonstrate that in post-menopausal women with positive breast cancer -- ER-positive breast cancer, who are poor metabolizers, at an increased risk for breast cancer recurrence?

Any comments?

DR. JUSKO: I agree with Mary's interpretation. I think it should be made clear that there can poor metabolizers because of genotype or because of drug

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interactions, and I think the language could be very specific about both sources are a problem.

DR. RAHMAN: And see whether we can make it a poor metabolizer genotype plus --

CHAIRMAN VENITZ: Right.

DR. RAHMAN: -- phenotype, and we could change it.

CHAIRMAN VENITZ: And my impression is based on the majority of the comments that the majority opinion is that it should include both. Scream if I misrepresent the Committee's feelings.

Okay. So I'm proposing then to either add that or on the record --

DR. RAHMAN: Okay.

CHAIRMAN VENITZ: -- that poor metabolizer includes genetic or drug interaction.

Okay. Let's discuss the merits of the question. In other words, is there sufficient evidence presented to us to draw this conclusion that there's increased risk? Any discussion? Mary.

DR. RELLING: I guess I would echo what Marie said. I think the way the question is worded, yes, there is clinical evidence, and I think that the trial that we heard the most

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about is definitely the cleanest clinical trial, a very good look, a very careful look at a relatively homogenous group of women, but you would obviously like more than one trial to feel more confident in this, but the way the question is worded, yes, I think the clinical evidence supports that, and the clinical evidence that sort of refutes it is based -- we talked about many limitations to that trial, so I can now see that the first two trials that were presented in the first presentation that are negative for an association of 2D6 with cancer recurrence have some methodologic problems that de-weight them considerably.

But it's still pretty small numbers.

DR. KAROL: Yeah, I think we've seen one good study that indicates that the clinical evidence supports this, but rather than saying that it demonstrates, I would say suggests that post-menopausal women -- I would like to see more studies with more subjects.

DR. RAHMAN: I'd like to remind the Committee that we have also mentioned about two other trials: the Italian Chemo Prevention Trial, which has been reported as a correspondence to the JCO, is coming out, and that is

indicating towards the similar results that we have seen
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with Dr. Matthew Goetz's paper, and the other -- that is the overall, but I'm kind of -- yeah, that's not exclusively post -- but that is in the adjuvant setting, yes, but they are both pre- and post-menopausal women there.

CHAIRMAN VENITZ: Okay.

DR. RAHMAN: And the other trial or retrospective analysis that will be coming out from a group from Germany -- Michel Eikelbaum's group, who are -- who have studied 400 patients and indicated that their results are supportive of what we have presented here in Dr. Goetz's presentation. So these are coming out. These are just kind of in there. There again, a similar kind of retrospective analysis of trials that was conducted a couple of years ago.

DR. LESKO: Yes, I'm trying to follow sort of the thinking process of the group, and on hand, there was a consensus that genotype and drug interactions ought to be linked together because they both produce and affect poor metabolizers.

In the reflection on need for additional clinical studies, am I sort of sensing that people are comfortable with the evidence on drug interactions, and that's a different standard of evidence than the evidence on
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genotype? In other words, we have a study that's prospectively done with hundreds of patients on the genotype. We often times will do a 24-subject stud on drug interactions, for example, and then find out a difference in area under curve occurs, and we're very comfortable with putting that small study result into the label.

So I'm not understanding how if we want to connect these two together for considering poor metabolizers as both drug interactions and genotype, do we want to separate them? In other words, is there more studies needed on drug interactions as well as genotype?

DR. WATKINS: Just sitting here and thinking about it, I've -- I'm someone who educates physicians on pharmacogenetics and drug interactions, and the concept of genetic deficiency, where there's a test for the enzymes always gone is easy to convey. The phenocopying of the poor metabolizer in drug interactions is a more difficult concept to convey, and it seems to me that's relevant in dividing the two when you discuss it, and assuming it goes on the label is to talk about a genetic deficiency, and then under drug interactions say that there are drug interactions that interfere with this enzyme and can produce a state close to
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the total deficiency, but it -- you know, it just seems to me the two are separate concepts and are easier to convey as two separate concepts.

CHAIRMAN VENITZ: Since I started this mess, I think that's relevant to the sub-question that I think we are going to discuss in a minute, in terms of what the label should look like. But I still consider the overarching question here, and that is do we -- does this Committee believe that we have seen sufficient clinical evidence to

convince us that poor metabolites, regardless of where the metabolizer comes from, whether it's genotype or phenotype that they are at an increased risk for breast cancer recurrence. And my answer to that question is yes, and it's based on the prospective study that I think we heard about today in very great detail.

But I will point out, again, if you look at the multivariate analysis originally just based on genotyping, there was no statistical difference after correcting for other prognostic factors. And I think you heard before that people are concerned about other prognostic factors imbalances in your populations that you're looking at. And you're still looking at small numbers.

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The only way or the only reason why in today's presentation we found that the multivariate analysis was statistically positive on the -- at least two major outcomes, not the overall survival -- was the fact that in addition to the genotype, the drug interactions were considered.

That's the reason why in my mind they are linked, because that's the evidence that I've seen today, which is, to me, personally convincing evidence.

DR. LESKO: Yeah, I think it's accurate the way you've pointed out. The P-value on the data that was based on genotype alone from the analysis of, you know, the 200 subjects in study, let's say 2 -- what was that study. Yeah, the 52 study, if you look at the relapse-free time, which was a collective endpoint, I think that was done based on genotype alone. That was not a combined genotype plus drug interactions in it.

CHAIRMAN VENITZ: I thought we have --

DR. LESKO: That would be on page nine, the graph on the bottom of my handout.

CHAIRMAN VENITZ: And I'm looking at the original reference, page nine, 316. That's where Dr. Goetz presented

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both the unadjusted and the adjusted analysis of the Cox Hazard Model. As he pointed out, when he spoke up a couple of minutes ago, if you look at the unadjusted so he is not considering any other prognostic factors, you do see that the genotype makes a difference in terms of relapse-free time and disease-free survival time. The P-values are less than 0.05 and the confidence level does not include one as far as the Hazard ratio is concerned.

But one you start accounting for prognostic factors that may have been imbalanced in comparing the population of wild-type versus non wild-type, then that significance disappears. Okay.

DR. GIACOMINI: But it's a difference between the univariate and the multivariate analysis is the difference.

CHAIRMAN VENITZ: Right. Yeah, and I'm saying to me the multivariate is the more relevant one because I have a whole bunch of other prognostics factors, some of which we don't even know about, and we have to account for that.

So I'm looking at the multivariate analysis to me as my gold standard, and I'm saying if you don't account for

the drug interactions, there is no statistical difference, even though the trend goes obviously the way you'd expect it to.

But we've already heard about the small sample size. The presentation today updated that information. It did include additional prognostic factors, and it did include the drug interaction, and those, if you look at the effect size, they're actually very similar.

DR. LESKO: So you're looking at the 2006 results in terms of outcome by metabolizer?

CHAIRMAN VENITZ: The adjustment -- the multivariate analysis is what I'm looking, because that to me is the most important one. It's table three, at the bottom of page 9316.

DR. CAPPARELLI: It's also on page 11 of the handout, but I think you brought up a key point as well is that really the magnitude of the effect is similar between the two studies.

CHAIRMAN VENITZ: Right.

DR. CAPPARELLI: So really what I see out of the additional analysis looking at the additional factors is you're removing noise. I mean I think the signal is clearly there and is, you know, in a prospectively collected manner that, you know, it's really the fact that you're getting rid of noise and it's not due to some other factors. And so really it is this poor metabolizer status that is sort of driving this thing, even in -- without the drugs that are there. It's just the issue that there's more noise.

CHAIRMAN VENITZ: Well, then, let's look at the data that we have seen from Dr. Flockhart's lab, where they look at the exposure differences, and the exposure differences in terms of the Endoxifen metabolite exposure comparing the different genotypes, the R-squared was .25, and again I think it's on one of the slides, so that means only 24 percent of the over variability in exposures -- so we're not looking at outcomes now -- is accounted for by genetics.

So what about the other, what is it 70 something percent?

DR. CAPPARELLI: Twenty-four percent is high actually.

CHAIRMAN VENITZ: Well, but remember what you are asking us to consider whether we have sufficient evidence, and I'm saying in my mind I cannot link the two. I cannot unlink the two.

DR. LESKO: I would just point out, too, there's -- in relabeling products, linking them together to account for poor metabolizer status is something we would deal with in a way in which the information would go in labels in different sections of the label.

CHAIRMAN VENITZ: I'm still --

DR. LESKO: Yeah.

CHAIRMAN VENITZ: -- overall question.

DR. LESKO: I understand.

CHAIRMAN VENITZ: I'm still on that point.

DR. MORTIMER: I guess my problem with this is not that I don't believe that it's Endoxifen and that inhibition with other agents is affecting. My problem is with the robustness of the data, and since, you know, the first trial that Dr. Goetz published really is a retrospective level one kind of trial, I feel much more comfortable with that data than going back and trying to collect drug information -- concurrent meds, which you know are notoriously difficult to rely on.

And the other problem I have is that the most -- the majority of my 20 plus year career is I have believed that hydroxy-Tamoxifen was the most important anti-estrogen, and so it's been with the last 10 years that we identify Endoxifen, and I guess until we have that data that says it

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is Endoxifen, how do we know it's not some other factor that we have yet to identify?

DR. BARRETT: I think the thing that we're all struggling with is the -- what we're calling clinical evidence here is not really specifically defined, and if you view this in the context -- I mean what we would like to have if we were writing the best labeling we could would be the results of the prospective study, where you would have adequate sample size and in a well-defined study with, you know, pre-constructed hypotheses you could derive the kind of statements, but you know now, again, Dr. Flockhart mentioned how far away from good labeling we are because this agent is so old when the original labeling was put together.

But I don't think I'm drinking the purple grape juice in looking at all of this data in the composite and saying that, you know, there seems to be reasonable evidence to -- reasonable clinical evidence. It does require you to at least make these kinds of bridges. There are some assumptions here, but if I was going to do this from scratch in terms of constructing a dose exposure relationship where you would rank all of these potencies -- I mean you do have

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information about the potencies of these various moieties, and I, you know, respect the comment that, you know, perhaps in the past when this kind of discrimination wasn't available whereas an improper association of the relevant moieties to clinical outcome, but I think you do know a lot more now than you did a while ago, so -- but I don't think clinical evidence here is going to come from a single study where you can point to that P-value and feel good about the sample size. It's just not there. So that's it.

DR. MCLEOD: Larry, I think one of the reasons why you're seeing some hesitancy around the table, at least, well, I can only speak for myself, is we're looking at this in two different directions. One is looking at it from the standpoint of constructing clinical guidelines, and there isn't enough data to construct those, but that's also not our remit.

If you look at it from detecting risk signal and changing the package insert in terms of risk, I think there is sufficient data to indicate there is a patient sub-group

that has a risk of a bad -- of outcome, and that is what I think we need to act on. And the rest of the information that will make us more comfortable with constructing

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clinical guidelines will not only follow, but also will not be developed by this Committee in the first place.

DR. RELLING: Yeah, I guess I just wanted to say that I think it's not absolutely necessary that the further clinical trial evidence that will make everyone feel more comfortable that the association between 2D6 poor metabolizer status and recurrence is real, it doesn't necessarily have to come from a new prospective study.

And I was trying to gather from everything that Dr. Goetz and others said, are there other retrospective analyses given all the huge breast cancer trials that have gone on in this country and in Europe over the last five or 10 years where we could gather together another uniformly treated group of ER-positive patients and get additional evidence that would be an independent clinical trial?

I think the one trial that's been presented has been carefully analyzed and we've talked about it enough. I can show you plenty of single clinical trial with more patients than this that would support other polymorphisms, but I wouldn't put forward changing the package insert based on that without independent confirmation in another trial.

So will that evidence be forthcoming soon from some

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other trials?

DR. FLOCKHART: So we have a large number -- sorry. I'm Dave Flockhart from Indiana University. We have a large number of other trials in process at the moment. I think the most valuable thing we might be able to do prospectively would be a metastatic trial, so where we find out relatively quickly where the patients respond to Tamoxifen and a genotype-controlled trial conducted prospectively in this country would be possible with one of the cooperative groups.

Now having said that, there are a large number of examinations of retrospective data that are currently ongoing. These include examinations of the IES trial, the International Exomestane Trial, which is Exomestane versus Tamoxifen trial. They include examination of the ATAC trial data. They include data looking retrospectively into studies in Australia; the retrospective examination of the prospective trial conducted in Italy, the Italian Chemoprevention Trial, and last but not least this thing that's been referred to several times about Michelle Ikenbaum's data, which is a retrospective look just at German cancer patients treated with Tamoxifen, and that has

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been conducted, and we have only rumors to really suggest that that -- because we can't examine the data.

So there's a lot of data that would be relevant to something like an ASCO guideline in terms of what to do with this.

But I'd submit to you but this is not an ASCO guideline committee. This is a label committee.

DR. MORTIMER: I would also argue in the question that if we're -- that we perhaps take out women with ER-positive breast cancer. My concern is who uses Tamoxifen right now. It's, you know, variably used in ER-positive breast cancer because the Aromatase inhibitors are sort of supplanting it because of acute toxicity profile, but the population of chemoprevention of women who have ductal carcinoma in situ, of people who have lobular carcinoma in situ, my guess is that's the largest population, and those people we may not have estrogen receptor status on them, and so if they're adversely affected, and they are going to be on a drug for five years, I think that's a bigger issue.

DR. PAZDUR: I just wanted to kind of frame this in a regulatory perspective.

You know we always look at a risk-benefit association

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here, and I think one of the speakers was getting at that.

You know, let's face it, this is less than a perfect dataset, okay, but we live in a less than perfect world in making regulatory decisions. So I guess we have to take a look at it from a risk-benefit association. We're not talking about the approval of a drug here, and basically I would almost look at this in the context of some of the decisions when we take a look at drug safety, where we don't have a lot of information, but we're compelled to make a decision, and lack of efficacy in a population truly is a safety issue, if you're denying people effective drugs that even could be considered a safety issue in a context -- in that context.

But from a risk benefit association, or a discussion period of time, if somebody has this information in the label and does not get Tamoxifen, they have the alternative of getting an AI, which may be in many minds a better therapy for people.

So from a risk-benefit association, you know there isn't a major issue here that I could see, unless somebody would like to comment on that.

You know, here again, everybody would like to have two

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prospective randomized trials here with this as the primary endpoint of the trial. With all of this pharmacogenomic data that we're getting whether we talk about the Cumatin label, whether we talk about 6MP, whether we talk about Irinotican, most of these are being done by investigator community trial-the investigator community or the academic community rather than drug companies. We're not going to have these large randomized trials, so we're not going to have these perfect databases.

So we're compelled to look at this in a risk-benefit relationship of what is the advantage of having this in the label versus not having it in the label, and here again we live in a less than perfect world, and if it's not in the label, basically somebody potentially, you know, could be denied a therapy -- a choice of therapy. But the choices that are there, there is not an inferior necessarily regimen that one is getting on if it is in the label.

CHAIRMAN VENITZ: Okay. Any additional comments?

Okay. Dr. Relling.

DR. RELLING: I totally agree with what Dr. Pazdur just said, which makes the questions that were asked about are there any data at all about the other Aromatase

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inhibitors in CYP2D6 poor metabolizers, and there are not I believe. Well, unless -- are there?

CHAIRMAN VENITZ: I think we've beaten question number three to death. I think you've got some spectrum of opinion in terms of what the clinical evidence supports and what it may not support. Is that a fair statement?

Okay. Then assuming that I think we're leading more towards the yes part, can we look at the first sub-question, or is there any disagreement that overall we're leaning more towards yes than towards no. In other words, if we look at the sub-question one as opposed to sub-question two.

Okay. So now our sub-question is, let's assume we've seen sufficient evidence that poor metabolizer status puts patients at risk, should the Tamoxifen label include information about increased risk for breast cancer recurrence in those poor metabolizers that are prescribed Tamoxifen? Howard.

DR. MCLEOD: I wondered if either Rick or Larry or someone from the FDA could allow us to see what sort of terms they might want to propose in the package insert around this question. I was, you know, suggesting some term like that might come to mind, but I don't know what the

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minimum -- what the types of terms can actually be used in a package insert. I mean does it have to be definitive type term or can it be a possible pre-disposition type of term?

DR. PAZDUR: You mean more of a subjective terminology rather than you must do this?

DR. MCLEOD: Right.

DR. PAZDUR: Yes. You know there could be suggestions that present the data that this has been shown in a recommendation of a physician should be aware of this. We frequently do that because when a drug is approved, there's a lot of information that is not known about a drug and frequently we warn people that, you know, this information is not available, and they should use clinical judgment in making a decision, et cetera.

So, yes, it doesn't have to be a definitive statement. And here, again, this is a risk-benefit association or discussion that one should have about what is the value of that information being in the product label versus not being in the product label.

DR. MCLEOD: For almost every drug I guess except Tamoxifen, high bilirubin is an indication. Most of the time the data for high bilirubin being a problem is

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non-existent, but it's still there.

DR. PAZDUR: Well, as we've pointed out on numerous occasions, you know there are many areas that are in the product label that suggest modifications for age, and, you know, that just happens to be thrown in there, because it was put in the product -- the clinical protocol and has

really been very poor studied, but follows through the drug through the lifespan of that drug and we have no idea what -- and many times -- what the true benefit of that recommendation is. It's kind of a clinical judgment that people make.

But to have hard proof is sometimes lacking. It was what was in the protocol that a certain age was restricted from going on, and we just don't have that information.

DR. LESKO: Yeah, I think the other perspective is that re-labeling a product with new information is not all or none. What we put in the label in terms of the wording and where it goes in the label is driven by the evidence that's available.

So I think you've seen this with the prior discussions that we've had here, where for Irinotican we had data that suggest that we ought to put this in the dosage and

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administration section. For some other drug, we might put it in the clinical pharmacology section or some other drug maybe in the warning section.

So I think the evidence drives where and what we say in the label, not does it go in or not.

DR. BARRETT: Yeah, I think the way that, Chris, the question is written -- I mean I don't know how you can't conclude that it should be in there, because if you're willing to buy the first part of this that you see clinical evidence, then why wouldn't you want it in there. I mean we can talk about the details of how it gets in there and, you know, how conservative the statement is, but, as you pointed out, Larry, historically labels have come under criticism when the have been least informative. So this is an opportunity I think to -- if you feel compelled to actually put this in here regarding this association, then it actually should be worded correctly in terms of the magnitude of this risk.

CHAIRMAN VENITZ: I would concur with that, but I would also add there's an additional update in the label about the entire drug metabolism section that is relevant based on Dave's presentation.

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Right now, there's no mention of Endoxifen in there, forget the fact that we have some comparison in terms of the relative exposures. In addition to, I mean this question or sub-question I guess really deals with the increased risks, meaning the outcomes, and I'm saying there's additional evidence that we saw today, mechanistic evidence about activity of metabolites, exposures to metabolites, that are nowhere to be found in the current label.

So I think the label, the re-labeling language should go beyond just expressing the fact that we have a prospective study with all the limitations that we talked about that indicates it puts patients at risk.

DR. LESKO: Yeah, we've not been sort of ignorant to the drug interaction issue with the drug. We have discussions in a working group about the drug interactions and what to put in the label about that. So that process is underway.

What's new sort of today is the sort of the recommendation of the Committee to kind of think of these in the same light, both functionally doing the same thing to the patient in terms of increasing risk, both valuable information pieces that a physician or patient might want to know by using the drug.

CHAIRMAN VENITZ: The mechanistic piece of causality assessment? We just need data?

DR. LESKO: Right.

DR. MCLEOD: I think the data that Sally and others presented certainly support an update of the clinical pharmacology section, but I would also put forward that the data that's presented is at least as strong, if not stronger, than most of the risk signals identified in the dosage and administration section; and would encourage that information to be included in that section, and not only because that's one of the few sections that are likely to be read by most physicians, but it also is the section that is read by important non-regulatory bodies, such as those who reimburse for costs of testing. And so that's not maybe within our remit, but I think that conveying the information -- it needs to be in that section for multiple practical reasons.

DR. PAZDUR: Remember also when we discuss drug labeling, there's a party that is not here that is very important, and that is the commercial sponsor who has ownership over this label in a sense. So those discussions need to be had with the FDA and the commercial sponsor.

One of the reasons I think probably we're having this meeting is obviously it's a public meeting, and they need to hear the voices of the community to be pushed in order to do some of these changes, and I think your point as far as updating other parts of the label are important. If we are opening it up for label negotiations, those could be addressed also.

CHAIRMAN VENITZ: Any other comments? Then can I summarize that the feeling of the Committee is that the label should be updated to reflect this increased risk?

Nobody is in violent opposition to that; right? Okay. Then let's move onto the last question, question number four.

DR. RAHMAN: We are again asking the Committee to discuss the issue that is there sufficient scientific and clinical evidence to support revisions of the Tamoxifen label that recommends CYP2D6 genotype testing for post-menopausal patients before they are prescribed Tamoxifen for adjuvant treatment?

CHAIRMAN VENITZ: Any comments?

Let me stick out my head first. I'm not sure whether I would go as far as saying recommend. Okay. In other words, I think we should provide the evidence and leave it up to the judgment of the health care provider and I think what drives you more than anything else is Dr. Goetz's own statement that he basically refers to the patient, explains

to them what the evidence suggests and then have them at least help to decide whether they should undergo genetic testing.

But recommend to me would stipulate that we think it should be done. I think it should be discussed.

DR. MCLEOD: When we reviewed Warfarin last year, there was multiple studies from three different continents that found a similar finding, and in that case we were able to come down with stronger recommendations on, you know, from this Committee.

In this case with one very good and a lot of study circumstantial evidence, I don't think we could be at the point where we would recommend or -- which I think would be interpreted as band-aid testing prior to prescription of the drug. I think practically that will come out from guidelines that develop as more data is developed, but putting it in the right section with supportive information

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that this is a risk signal, I think is the way we should go forward in my personal view.

DR. RELLING: I guess my view is that if we accept three, then I accept four. I mean my problem is I didn't have strong objections to saying okay to three, but I have, you know, some objections because it's one trial. So that, to me, is the question -- to me, it's wishy washy. We as scientists and clinicians should be able to recommend to patients what to do. Patients should not have to make this decision. I mean, of course, they can make the decision themselves, but we should be able to recommend what the right decision is.

So to me, the problem is that the evidence for three is still only one study. If three were supported by more than one study, then I would wholeheartedly endorse three and, of course, I would endorse four.

The only reason -- so to me, since we've already said we don't have strong objections to three, then four should be there. Yes, we should recommend if we think that the evidence supports that 2D6 genotype can affect relapse risk from Tamoxifen, the patients should be tested for 2D6 genotype.

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CHAIRMAN VENITZ: Anyone else? Joanne.

DR. MORTIMER: I'm going to argue the adjuvant again. I mean if we're going to -- if we make the assumption that there is an impact, I think most of the people who are getting -- or a good chunk of the people who are being prescribed Tamoxifen are not the setting that Dr. Goetz's trial was done. It's more the Italian study. It's more the non-invasive cancers, so I'd argue to take out to recommend or consider testing in post-menopausal women who are prescribed Tamoxifen.

CHAIRMAN VENITZ: Howard.

DR. MCLEOD: There are currently seven indications for Tamoxifen in the context of breast cancer. Do the recommendations have to separately comment on any or all of those or -- as kind of a follow up to Joanne's comment?

I mean there's no data for --

DR. PAZDUR: Not necessarily. I think, you know, you have to look at the risk -- here, again, it's a risk-benefit association or discussion that we're having for each of these; okay? So you know it's what the data shows basically, and you know the overwhelming -- you know, would you consider a difference -- why should there be a

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difference in the adjuvant versus the metastatic disease? You know that needs to be discussed since we're dealing with basic pharmacology here and one would not expect a difference necessarily in the mechanism of action of the drug. But here again, the data may not be there in these specific areas, and then what would be the risk of making those decisions?

Here, again, you know, I think it's important that you realize that FDA does not mandate or does not control the practice of medicine on individual patients here, so, you know, generally if people have a data issue where they need further discussion that could be somehow stated in the label that, you know, it could be suggested that this test be done and further discussion needs to be had with the patient.

CHAIRMAN VENITZ: Ed?

DR. CAPPARELLI: Just one other point that if -- and I agree with putting some information in the dosing component that links to this, but if we put that there, it would be nice to have some reference as well to sort of phenotype, so, you know, in terms of assessment of 2D6 metabolism, because, as was pointed out earlier, that's where it's going to be read and the drug interaction stuff, which may

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actually be a larger part of the population, may get missed in terms of the SSRI drug interaction in particular, but other 2D6 inhibitors.

CHAIRMAN VENITZ: Kathy?

DR. GIACOMINI: Yeah, so I'm also concerned with one trial only.

On the other hand, I feel like the evidence with the mechanism, because there is -- often there is just an association with a snip and you have no idea what the mechanism is, and then I want replication studies. Here there's strong mechanism and a trial, and trials to become, so that's more persuasive to me with the biology to, you know, vote a little bit more or not vote a little bit more strongly.

Also, I guess from my point of view, adjuvant and those different modifiers I agree also that those should be removed right now, because we are dealing with what the pharmacology, and I don't see that there is any feeling, any rationale, at all for just specifying adjuvant therapy only or metastatic disease, especially again with the mechanism.

And then the thing that really concerns me is that if I were a patient, and this wasn't in the label, and then I

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wouldn't find this out, I mean that's what concerns me. That's why I feel like we should act now in a more positive way than have this not available in the product label so people aren't even aware of this potential for, you know,

for maybe you're not -- if you have a bad CYP2D6 genotype or you're on this drug and a bad CYP2D6, then you make a choice. You're sitting there with your physician and you make a choice to go on with -- and you shouldn't maybe. You should have made a different choice, and, although I know we should be telling patients with me and my physicians it's often a discussion. And I'd just like that information there.

CHAIRMAN VENITZ: Any additional comments?

DR. RAHMAN: Can I?

CHAIRMAN VENITZ: Yeah. Go ahead.

DR. RAHMAN: I wanted to mention about the availability of the test. In the past, we have approved recommendations in the label without -- with concerns about the availability of the test. And here, we have an FDA-approved test, and here we have tests that are available in national laboratories and other places, so people have easy access to this kind of test, if they wanted to get it.

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And in the label, we have many sections where we can put in recommendation about testing; one is the laboratory tests sections and the other is the dosage and administration sections.

So we have the choice of putting this information in some way to inform the patients and the physicians that there are tests available.

CHAIRMAN VENITZ: Paul?

DR. WATKINS: Just one other issue I think to put it to rest, but since people on potent 3A inducers would phenocopy as a rapid metabolizer so that we already know that in the real world genotype won't correlate with phenotype exactly. What actually is the feasibility -- it was brought up before of Endoxifen plasma level since as I understand it everything has a long half life. It wouldn't even matter when in the day you measured a sample. And is that -- I mean I think it wouldn't be economically feasible, but compared to 300 buck, I mean does how that stack up?

DR. FLOCKHART: Well, without commenting on that as a surrogate, those are -- inducers would lower Endoxifen concentration. Again, so I -- but we have very, very little data really to support that, Paul.

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We have I think maybe three patients -- three patients taking heavy inducers, and we haven't studied it formally. We would like to study it formally.

The other thing I think relevant to Dr. Pazdur's comments about risk-benefit analysis, I think risk-benefit is not the same for all patients on Tamoxifen, because some people have choices and some people don't.

Post-menopausal patients have a wide range of Aromatase inhibitor choices. Pre-menopausal patients just have a much, much more limited series of choices. So I actually think you have to separate out the patient population in talking about risk benefit.

CHAIRMAN VENITZ: Paul?

DR. WATKINS: Just so to get back to the question, so if there are 500,000 women on Tamoxifen now, it would seem

to me it would make more sense to measure their Endoxifen levels than to CYP2D6 genotype them, because that will tell you their relevant phenotype, or am I missing something?

DR. FLOCKHART: We don't have any study where we've taken Endoxifen concentrations and correlated them with outcome. That's a problem. We have Endoxifen concentrations with bone density; Endoxifen concentrations

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with platelet change that correlates, that makes sense. But we don't have Endoxifen concentration with outcome, to be honest this is rather like what Howard was talking about before, I don't see that happening. You need thousands of patients to do that kind of thing. I don't see it happening in the foreseeable the future.

DR. WATKINS: Is the assay difficult or?

DR. FLOCKHART: No, no, no. No, absolutely, it is not a difficult thing to do and what you say pharmacologically is absolutely true: the concentrations do not do this. They're very smooth, so I think most likely it is a pretty stable thing.

DR. GOETZ: I'll just make one -- Matthew Goetz from Mayo Clinic.

[Laughter.]

In terms of the recommendation for testing Endoxifen, I think one of the key issues is that if we're going to put a patient on Tamoxifen, we need to know whether she's genotypically a poor metabolizer up front. And the reason is because I think there would be ethical issues of waiting, let's say, four to six months to get steady state levels and say okay now what is your Endoxifen level, when, in fact,

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her risk is greatest within those first two years.

So you're right, though, for let's say, for example, an extensive metabolizer or an intermediate metabolizer, where knowing this information after four to six months and, you know, subtle changes in Endoxifen may be important.

But from what we can see from poor metabolizers, their phenotype is really quite pronounced and Endoxifen are low really from the get go.

CHAIRMAN VENITZ: Larry.

DR. LESKO: Now, I think it's important for us at FDA to come away from this morning discussion with a recommendation from the Committee. In past Committee meetings, I have asked for votes on different issues, and we can't do that here, but I wonder if it would be worthwhile going around the table and asking for an opinion. What I've heard is somewhat of a mixed opinion: let's update the label; let's possibly recommend a test; let's probably update the label, but stop short of recommending a test. And I'd like to get a consensus by going around the table if you think it's a good idea, Dr. Venitz, and get each person to comment on the updating of the label.

CHAIRMAN VENITZ: Well, let me try to handle it

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without us --

DR. LESKO: Okay.

CHAIRMAN VENITZ: -- going through a vote.

DR. LESKO: I didn't say vote.
CHAIRMAN VENITZ: I know. I know. I'm going back now to sub-question one to question three, because I think that's where you start off.
I think we had maybe not consensus, but at least a prevalence of opinion that the label should be updated to reflect the increased risk, as well as additional mechanistic stuff that was presented to us today. Nobody is screaming at me. So I think we have consensus on that. Unanimous consensus.
Number four, I interpret what I heard, a divergence of opinion. Some of us feel the test, the genetic test, should be recommended. Some of us feel it should be presented in the label as an option, as being available to patients. And that's kind of the spectrum of opinion. I don't think we have consensus on that. Is that reflecting the Committee's -- does anybody disagree with that violently?
DR. MCLEOD: I think the other -- Howard McLeod. The other end of it is that I think all of us feel or most all

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of us feel that actions should be taken to put this information in the appropriate section of the package insert, so it's not just -- the nuance is how strong, whether it's require versus suggest. The nuance is not should it be there in the first place.
CHAIRMAN VENITZ: That's fair. Does that?
DR. LESKO: That answers my question.
CHAIRMAN VENITZ: Okay. Any further comments? I think we've done our job. I think we're ready to break for lunch. I'm asked to remind the Committee members not to discuss any issues amongst themselves. Everything has to be discussed in public. And we reconvene and start in -- what? Half an hour? We have a one-hour lunch break, so we reconvene at a quarter to two. At 1:45 p.m.
[Whereupon, the Committee stood in recess to reconvene at 1:45 p.m. the same day.]

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P R O C E E D I N G S

October 18, 2006 (Afternoon Session)

CALL TO ORDER

CHAIRMAN VENITZ: Can we please reconvene? Can the Committee please take their seats?

Okay. Welcome back from lunch everyone.

We are now starting our topic two, Evaluation of Transporter-Based Drug Interactions, and we're going to start our discussion by Ms. Phan giving the COI disclosure.

CONFLICT OF INTEREST DISCLOSURE

DR. PHAN: This is the Conflict of Interest Statement for Topic 2, Transporter-Based Drug Interactions.

The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

This meeting is being held by the Center for Drug Evaluation and Research of the Clinical Pharamacology Subcommittee of the Advisory Committee for Pharmaceutical Science will discuss and provide comment on the second topic, Evaluation of Transporter-Based Drug Interactions.

Unlike issues before a Committee, in which a particular product is discussed, the issue of product applicability, such as the topic of today's meeting involves many industrial sponsors, academic institutions.

The Subcommittee members have been screened for their financial interests as they may apply to the general topic at hand.

Because general topics impact so many institutions, it is not practical to recite all potential conflicts of interest as they may apply to each member.

In accordance with 18 USC 208B, full waivers have been granted for the following participants: Drs. Jurgen Venitz, Jeffrey Barrett, Edmund Capparelli, Marie Davidian, Kathy Giacomini, William Jusko, Jacob Mandema, and Paul Watkins.

Waivers documents are available at the FDA document Web site. Specific instructions as to how to access the Web page are available outside today's meeting room at the FDA Commission table.

In addition, a copy of all waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30, at the Parklawn Building.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the Committee, these potential conflicts are mitigated.

In the event that discussion involves any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or

previous financial involvement with any firm whose products they wish to comment on.

CHAIRMAN VENITZ: Thank you, Mimi.

Our first presenter is going to be Dr. Shiew-Mei Huang. Dr. Huang is the Deputy Director for Science in the Office of Clinical Pharmacology, and she's going to introduce Topic 2.

KEY ISSUES IN THE EVALUATION OF DRUG INTERACTIONS

DR. HUANG: Thank you, Jurgens, and good afternoon.

Our focus this afternoon will be on transporters and their role in drug interactions.

I will discuss the critical messages of the draft guidance on drug interactions, which was published last month, focusing on the progress and our recommendation between the CYP-based or transporter-based interaction.

And I'll discuss in more detail our proposed method to evaluate transporter-based interactions and I'll give some recent labeling examples, followed by questions for the Committee.

The FDA has issued guidance on drug interactions about nine years ago, first on in vitro evaluation, and followed